IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	
	:	
Jacobus M. LEMMENS et al.	:	Examiner: KISHORE, Gollamudi
	:	
Serial No.: 10/024,520	:	Group Art Unit: 1615
	:	
Filed: December 21, 2001	:	Atty Docket: SYN-0011

For: AMLODIPINE FREE BASE

TRANSMITTAL OF APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

January 20, 2006

Sir:

Further to the Notice of Appeal filed July 20, 2005, applicants submit herewith an Appeal Brief under 37 C.F.R. § 41.37. Please charge the Appeal Brief fee under § 41.20 in the amount of $500.00 to Deposit Account No. 50-2877.

Please charge any shortage in fees, or any overpayment, in connection with this filing, including extension of time fees, to Deposit Account No. 50-2877.

Respectfully submitted,

Mark R. Buscher, Reg. No. 35,006

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PATENT

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APPEAL BRIEF

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P.O. Box 1450
Alexandria, VA 22313-1450

January 20, 2006

Sir:

Further to the Notice of Appeal filed July 20, 2005, and the enclosed petition for a four (4) month extension of time, appellants hereby submit the Appeal Brief in connection with the above-identified application. Authorization to charge the Appeal Brief filing fee in the amount of $500.00 is also attached. Entry and consideration of this Brief are requested. For the reasons set forth hereinafter, reversal of each of the Examiner's rejections is respectfully requested.

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Table of Contents

I. Real Party in Interest

The real party in interest is Synthon IP Inc., a corporation of Virginia, which is one of several privately held companies ultimately owned by Synthon Holding BV, a corporation of The Netherlands.

II. Related Appeals and Interferences

There are no appeals or interferences, previously or currently, that are related to this application.

III. Status of Claims

Claims 1, 3-10, 12, 35-37, 39-43, and 49 are rejected.

Claims 2, 11, 13-34, 38, 47, 48, 50, and 52 have been cancelled.

Claims 44-46 and 51 are withdrawn from consideration.

IV. Status of Amendments

No amendments after the final rejection have been filed. Accordingly, the claims remain as rejected in the final office action of February 23, 2005.

V. Summary of Claimed Subject Matter

The present invention relates to pharmaceutical tablets that contain amlodipine free base as an active ingredient and that exhibit relatively low punch residue. Claims 1 and 43 are independent.

Claim 1

Independent claim 1 recites a pharmaceutical tablet composition comprising an effective amount of amlodipine free base and at least one pharmaceutically acceptable excipient. The amlodipine free base is selected from crystalline Form I, crystalline Form II, and mixtures thereof. The tablet also exhibits a low punch residue in that the average residue of amlodipine on the tablet punch is 0.7 $\mu g \cdot cm^{-2}$ or less per tablet. Support for claim 1 can be found on page 3 lines 4-8 (overall composition); page 4 lines 20-32 (low punch residue defined); page 5 lines 23-24 (crystalline Forms I and II); and page 6 lines 4-5 (mixture of Forms I and II) of the specification.

Claim 43

Independent claim 43 is similar to claim 1, but with two differences. First, the preamble in claim 43 further recites that the tablet is an oral tablet. Secondly, the Markush group of amlodipine free base forms in claim 1 is replaced by requiring "crystalline" amlodipine free base to be contained in an effective amount. Support for claim 43 can be found as expressed above for claim 1 as well as on page 2 lines 23-24 (oral dosage); page 5 line 23 (any form); and page 8 lines 4-8 (crystallization of amlodipine free base) of the specification.

Dependent Claims 8 and 49

Claims 8 and 49 require the amlodipine free base to be crystalline Form I amlodipine free base. Support for these claims includes page 5 line 23 of the specification.

VI. Grounds of Rejection to be Reviewed on Appeal

1. Whether claims 1, 3-10, 12, 35-37, 39-43, and 49 are unpatentable under 35 U.S.C. § 103(a) over U.S. patent 6,057,344 (Young).

2. Whether claims 1, 3-10, 12, 35-37, 39-43, and 49 are unpatentable under 35 U.S.C. § 103(a) over U.S. patent 5,155,120 (Lazar) in combination with U.S. patent 4,879,303 (Davison).

3. Whether claims 1, 3-10, 12, 35-37, 39-43, and 49 are unpatentable under 35 U.S.C. § 103(a) over U.S. patent 5,155,120 (Lazar) in combination with U.S. patent 6,057,344 (Young).

VII. Arguments

The present invention relates to the unexpected discovery that amlodipine free base can be used to make pharmaceutically acceptable tablets without encountering excessive stickiness. Amlodipine was originally developed by Pfizer Inc. (see U.S. patent 4,572,909). The free base form of amlodipine was not isolated or precipitated in U.S. 4,572,909. Instead amlodipine was isolated as a salt, with the maleate salt of amlodipine being the most preferred. Subsequently amlodipine maleate was found to suffer from tabletting and stability problems and so a switch to the besylate salt of amlodipine was made, as described in U.S. patent 4,879,303 (Davison)[1]. As part of the basis for patentability in selecting the besylate salt from the genus of salts disclosed in the earlier original amlodipine patent, U.S. 4,572,909, the Davison patent recites a study regarding the relative stickiness of tablets containing various amlodipine salts as well as the free base; i.e. the non-salt form of amlodipine. While the besylate salt achieved an average of 1.17 $\mu g \cdot cm^{-2}$, the amlodipine free base achieved a much higher value of 2.02 $\mu g \cdot cm^{-2}$ meaning that the free base amlodipine tablet was more sticky (see Davison col. 3 line 30 et seq., including Table 2 in col. 4). Accordingly, the prior art from the original drug proprietor taught the artisan that amlodipine free base tablets were relatively sticky to the tabletting punches and thus would be more problematic than the besylate salt-containing tablets.

Surprisingly, the instant appellants discovered that amlodipine free base tablets can have a low punch stickiness; even lower than the punch stickiness of the besylate salt

[1] The besylate salt of amlodipine was ultimately commercialized by Pfizer under the brand name NORVASC®

of amlodipine-containing tablets. This unexpected result is required in both independent claims 1 and 43 by the recitation "wherein said tablet leaves an average residue of amlodipine on the tablet punch of 0.7 $\mu g \cdot cm^{-2}$ per tablet or less." Thus, by definition, the presently claimed invention achieves unexpectedly low punch residue; lower than previously expected and even lower than tablets containing the commercialized besylate salt of amlodipine.

To help achieve this low punch residue, the presently claimed invention also requires that the amlodipine free base must be crystalline. This is also a further distinction over the applied prior art.

While Davison does not describe how the amlodipine free base used in the stickiness experiment was obtained or whether it was crystalline or not, a more recent Pfizer Inc. patent seems to shed some light on the situation. According to U.S. Patent 6,680,334 to Bentham et al., crystalline amlodipine free base was not disclosed in Davison and is considered by Bentham et al to be novel.[2] Bentham et al. also review several other prior amlodipine-based patents, including U.S. 6,057,334 to Young which is applied by the Examiner, and conclude that none of them teach forming a crystalline amlodipine free base. Interestingly, Bentham et al. teach that "[i]n fact, solid free base initially synthesized by the present applicants 'in-house' was characterised as a poorly soluble and low-melting point material, which was unsuitable for formulation." US 6,680,334 at col. 2 lines 26-29. Given that both Bentham et al and Davison are Pfizer

[2] Curiously, Bentham et al., which was filed after the instant application, has already been issued and with broader claims than the present application, including a claim to crystalline amlodipine free base per se. While not binding on the USPTO, it is "informative" that at least some experts at the USPTO would apparently find the instant claims allowable solely upon the recitation of crystalline amlodipine free base.

Inc. patents, it seems likely then that the amlodipine free base of Davison was a non-crystalline material.

Prior to Bentham et al, which is not prior art to the present application, many patents described amlodipine, but none of them taught or suggested crystalline amlodipine free base. In this sense, the applied prior art is cumulative, at best, with the teachings in US 4,572,909 or Davison. None of them deal with crystalline amlodipine free base nor address the known prior art problem of stickiness with amlodipine free base tablets. Accordingly, each of the Examiner's rejections fails to render the instant claims obvious within the meaning of 35 U.S.C. § 103. The errors in each rejection are specifically addressed below.

1. Rejection over Young

Claims 1, 3-10, 12, 35-37, 39-43, and 49 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. patent 6,057,344 (Young). Appellants respectfully submit that this rejection is in error and request reversal thereof.

Young relates to the use of optically pure (-) amlodipine in treating hypertension and angina. Unlike the commercially used besylate salt of amlodipine which is a racemate, Young administers only one amlodipine isomer in order to reduce adverse effects.

Young explains how to synthesize the individual isomers of amlodipine in columns 9 and 10. The technique involves forming a cinchonidine salt of an azido precursor of amlodipine and separating the formed diastereomers via fractional crystallization. In this regard, column 10 lines 2-5 reports that "a crystalline precipitate is formed" which can be "recrystallized to constant rotation to give the diasteromerically

pure cinchonidine salt 2." Initially the Examiner believed this passage to refer to the formation of crystalline amlodipine, but apparently the Examiner now agrees (and properly so) that this passage is only referring to the crystallization of a ***salt*** of an amlodipine ***precursor*** and not to amlodipine free base. The synthesis continues by treating the resolved cinchonidine salt with acid to form the now optically pure azido precursor; esterifying the azido precursor; and reducing the azido group to an amine to thereby form optically pure amlodipine. But the formed optically pure amlodipine is not crystallized as the free base. Instead, Young states in column 10 lines 17-18 that the resulting (-) amlodipine "is most conveniently isolated as the salt of an acid, e.g. as the maleate 5."

The Examiner relies on Example 8 in Young, which recites a recipe for three strengths of tablets containing (-) amlodipine. The amount of the active ingredient, (-) amlodipine, is stated in the first line of the table for each of tablets A-C, namely 0.5, 2.5, and 5.0 mg. Putting aside whether Example 8 is a generic hypothetical formulation for use with any salt of (-) amlodipine, as appellants believe[3], or, a working example that actually uses (-) amlodipine free base, as the Examiner believes, Young still fails to render obvious the claimed invention. Specifically, Young fails to (1) teach the use of ***crystalline*** amlodipine free base and fails to (2) provide a reasonable expectation of successfully obtaining the appellants' claimed low punch residue.

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[3] Young uses the word amlodipine to also mean salts of amlodipine. For example, col. 2 lines 1-6 at first refers to the only commercially available amlodipine as being a racemic mixture, but then clarifies that that commercially available racemic amlodipine is actually the besylate salt of amlodipine. Similarly, col. 11 lines 31-50 refer to making the pharmaceutical compositions with "(-) amlodipine"; yet the reader (and the Examiner) would hardly argue that Young intended that only amlodipine free base can be formulated this way and that the salts of (-) amlodipine are either excluded or formulated some other way. See also the usage of "amlodipine" in Lazar, discussed *infra*. Thus, in Example 8 the reference to (-) amlodipine would be understood as a generic recitation of any (-) amlodipine or its salt.

Nowhere in Young is crystalline amlodipine free base taught. Indeed, Young teaches away from even trying to isolate amlodipine as free base by indicating that such isolation is not convenient; i.e., amlodipine is "most conveniently isolated as the salt of an acid." Such a teaching hardly suggests the formation of crystalline (-) amlodipine and instead connotes that either a difficult technique or an unhandy product results from attempting to isolate the free base form. In as much as the prior art as of Young's filing date did not mention, teach, or describe crystalline amlodipine free base and that Young is equally silent, the Examiner has no basis to assume that (-) amlodipine free base would be (or even could be) crystalline. Without any teaching in the applied prior art of crystalline amlodipine free base, the Examiner lacks proper motivation to find the use of crystalline (-) amlodipine free base to have been obvious in Young Example 8.

Furthermore, the Examiner has failed to explain why such a composition would be reasonably expected to exhibit the claimed low punch residue. Instead, the Examiner attempts to improperly place the burden on appellants to prove that (i) the amlodipine free base used in Young is amorphous; (ii) that the tablets of example 8 do not have the claimed punch residue; and (iii) the criticality of the claimed punch residue range. Setting aside the fact that it is impossible to replicate Young Example 8 because the formation or type of (-) amlodipine free base is not disclosed by Young, the burden is initially on the Examiner to justify why any amlodipine free base tablet would be reasonably expected to exhibit the appellants' claimed low punch residue. Considering the prior art as a whole, including the negative teachings in Davison, the Examiner has no basis to contend that the Young Example 8 tablets would exhibit or could be modified to exhibit a punch residue of less 0.7 $\mu g \cdot cm^{-2}$. By the time of Young, the art already knew,

via the disclosure in Davison, that amlodipine free base makes stickier tablets than the besylate salt of amlodipine. Nothing in Young changes that understanding. But the present invention is unexpectedly superior to that understanding.

For instance, Example 9 of the present specification shows that a crystalline amlodipine free base containing tablet (using Form I from Ref. Ex. 3) can have an average residue of only 0.55 $\mu g \cdot cm^{-2}$ while the comparison amlodipine besylate containing tablet has an average residue of 1.16 $\mu g \cdot cm^{-2}$. The besylate salt tablets' value is almost identical to the value reported in Davison (1.17 vs. 1.16), but the crystalline amlodipine free base tablets are dramatically less sticky (from 2.02 down to 0.55) in comparison to the free base tablets reported in Davison; and less sticky than the amlodipine besylate tablets. Claims 1 and 43 recite and require this less sticky condition in order to be within the scope of the present invention, e.g. reciting an amlodipine average punch residue of 0.7 $\mu g \cdot cm^{-2}$ or less.

Having demonstrated and claimed low punch residue, the Examiner has failed to satisfy his initial burden in explaining why it would have been obvious, at the time of the present invention was made, that amlodipine free base tablets could have been made having the claimed low punch residue.

Lastly, appellants have submitted comparative test data that directly shows that the form of the amlodipine free base can have a significant effect on the stickiness of the tablets. A copy of the executed declaration under 37 CFR 1.132 of Arlette Vanderheijden (the Declaration) filed April 16, 2004, is attached hereto in the Evidence Appendix. In the Declaration three crystalline and one amorphous form of amlodipine free base were attempted to be tabletted using the same formulation and methodology as in Davison.

The amorphous material could not be formulated/blended and thus could not be tabletted at all. The Form I and Form III crystalline amlodipine free base tablets exhibited very low punch residue while Form II gave higher punch residue and was outside the scope of the instant claims. Thus, the form of the amlodipine free base does affect the stickiness. Crystalline amlodipine free base, especially Form I, can help provide low punch residue. Nothing in Young suggests such a result. In the absence of any guidance in Young about selecting a crystalline form of amlodipine free base or any discussion about (-) amlodipine free base having improved stickiness to tablet punches, the presently claimed invention is not suggested or rendered obvious by the teachings of Young.

In summary, Young fails to teach or suggest the formation of an amlodipine free base tablet containing crystalline amlodipine free base or having a low punch residue and thus fails to establish a *prima facie* case of obviousness of the presently claimed invention which has both features. Further, in view of all the evidence, the formation of an amlodipine free base tablet having low punch residue was unexpected and surprising. Having required a *per se* unexpected and unobvious result in the claims, the rejection under § 103 based on Young is improper and must be reversed.

(a) Claims 8 and 49 are further patentable over Young

In addition to the above reasons, claims 8 and 49 are further patentable in that each recites that the crystalline amlodipine free base is crystalline Form I. Young fails to teach or suggest this specific crystalline form. Thus, it would be further unobvious to select Form I crystalline amlodipine free base for use in a tablet over the teachings in Young.

2. Rejection over Lazar in Combination with Davison

Claims 1, 3-10, 12, 35-37, 39-43, and 49 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. patent 5,155,120 (Lazar) in combination with U.S. patent 4,879,303 (Davison). Appellants respectfully submit that this rejection is in error and request reversal thereof.

Lazar generically teaches the use of amlodipine and its salts for treating congestive heart failure. Although the example in the patent refers to "amlodipine" as the active ingredient, column 3 lines 29-31 clarify that "the following example w[as] conducted with amlodipine benzenesulfonate" which is also known as amlodipine besylate. Thus, a composition containing amlodipine free base was not made or used in Lazar. Indeed, Lazar fails to teach crystalline amlodipine free base.

The Examiner asserts that Lazar renders obvious a pharmaceutical composition containing the appellants' claimed crystalline amlodipine free base. However, the Examiner's rejection fails to allege that this supposedly obvious composition would have the claimed low punch residue. Indeed, the Examiner has refused to recognize that the independent claims recite an unexpectedly low punch residue of 0.7 $\mu g \cdot cm^{-2}$ or less. Instead, the Examiner continues to declare that in the absence of unexpected results, the claims would have been obvious and attempts to discredit the evidence in the Declaration. The Examiner's rejection is improper for at least two reasons.

Firstly, the Examiner has no basis or suggestion in the applied prior art to make or use a ***crystalline*** amlodipine free base in making the composition of Lazar. It is only by improper hindsight that the Examiner presumes that such would have been obvious; not by any identified teaching in the prior art.

Secondly, the Examiner has failed to appreciate that claims 1 and 43 recite a truly surprising and unexpected result vis-à-vis Davison; namely the claimed low punch residue. Appellants do not merely rely on the above-described showings in the specification and the Declaration for unexpected superiority in punch residue, but actually recite it as a claimed feature of the invention. The Examiner has no basis to assert that a crystalline amlodipine free base tablet would be expected to exhibit an average punch residue that is 0.7 $\mu g \cdot cm^{-2}$ or less (which is less than the amlodipine besylate tablets) given the teachings in Davison that amlodipine free base tablets exhibit an average punch residue of 2.02 $\mu g \cdot cm^{-2}$. The claimed low punch residue is an unexpectedly superior result over the prior art teachings. In the absence of a reasonable expectation of achieving such a low punch residue, the formation of the presently claimed invention could not have been obvious.

Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness. Neither the claimed crystalline amlodipine free base limitation nor the low punch residue limitation is found in the cited art. To the contrary, Davison teaches away from the surprising result claimed by the present invention. Therefore, the presently claimed subject matter is unobvious under § 103 and reversal of this rejection is requested.

(a) Claims 8 and 49 are further patentable over Lazar and Davison

In addition to the above reasons, claims 8 and 49 are further patentable in that each recites that the crystalline amlodipine free base is crystalline Form I. Lazar and Davison fail to teach or suggest this specific crystalline form. Thus, it would be further

unobvious to select Form I crystalline amlodipine free base for use in a tablet over the teachings in Lazar or Davison. Therefore, claims 8 and 49 are further patentable.

3. Rejection over Lazar in Combination with Young

Claims 1, 3-10, 12, 35-37, 39-43, and 49 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. patent 5,155,120 (Lazar) in combination with U.S. patent 6,057,344 (Young). Appellants respectfully submit that this rejection is in error and request reversal thereof.

The instant rejection is essentially cumulative with the above two rejections; the Examiner relying Lazar for disclosure of tablets with various excipients and Young for the alleged use of crystalline amlodipine free base. The combination does not overcome (nor is it purported to overcome) the basic deficiencies identified above in the Examiner's rejections. Specifically, neither Lazar nor Young teaches or suggests ***crystalline*** amlodipine free base and neither teaches or suggests an amlodipine free base tablet having an average punch residue of 0.7 $\mu g \cdot cm^{-2}$ or less. To the contrary, the prior art as a whole, including the teachings in Davison, lead the worker to believe that amlodipine free base tablets were too sticky and certainly stickier than amlodipine besylate tablets. Surprisingly, the present invention uses crystalline amlodipine free base and has an average punch residue that is less sticky than amlodipine besylate tablets. Such an unexpected result was clearly unobvious. Accordingly, for the reasons set forth above, the presently claimed subject matter is unobvious under § 103 and reversal of this rejection is requested.

(a) Claims 8 and 49 are further patentable over Young

In addition to the above reasons, claims 8 and 49 are further patentable in that each recites that the crystalline amlodipine free base is crystalline Form I. Lazar and Young fail to teach or suggest this specific crystalline form. Thus, it would be further unobvious to select Form I crystalline amlodipine free base for use in a tablet over the teachings in Lazar and Young.

7. Conclusion

For the reasons set forth above, each of the Examiner's rejections is in error and reversal thereof is respectfully requested.

Respectfully submitted,

Mark R. Buscher, Reg. No. 35,006

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Claims Appendix

1. A pharmaceutical tablet composition comprising an effective amount of amlodipine free base and at least one pharmaceutically acceptable excipient; wherein said amlodipine free base is selected from the group consisting of crystalline Form I amlodipine free base, crystalline Form II amlodipine free base, and mixtures thereof; and wherein said tablet leaves an average residue of amlodipine on the tablet punch of 0.7 $\mu g \cdot cm^{-2}$ per tablet or less.

3. The composition according to claim 1, wherein said excipient is a calcium phosphate.

4. The composition according to claim 1, wherein said excipient is microcrystalline cellulose.

5. The composition according to claim 3, which further comprises microcrystalline cellulose.

6. The composition according to claim 5, wherein said calcium phosphate is anhydrous calcium hydrogen phosphate.

7. The composition according to claim 1, wherein said amlodipine free base is crystalline form II amlodipine free base.

8. The composition according to claim 1, wherein said amlodipine free base is crystalline Form I amlodipine free base.

9. The composition according to claim 1, wherein said amlodipine is a mixture of crystalline amlodipine free base form I and form II.

10. The composition according to claim 1, wherein said tablet contains 1 to 100 mg of said amlodipine free base.

12. A method of treating or preventing hypertension, angina, or congestive heart failure, which comprises administering the composition according to claim 1 to a patient in need thereof.

35. The composition according to claim 1, wherein said amlodipine free base was incorporated into said composition in the form of particulates having an average particle size of at least 100 microns.

36. The composition according to claim 35, wherein said average particle size is 150-350 microns.

37. The composition according to claim 36, wherein said average particle size is 200-300 microns.

39. The composition according to claim 35, wherein said excipient is anhydrous calcium hydrogen phosphate.

40. The composition according to claim 36, wherein said excipient is anhydrous calcium hydrogen phosphate and said composition further comprises microcrystalline cellulose; and wherein said tablet leaves an average residue on the tablet punch of 0.6 $\mu g/cm^2$ per tablet or less.

41. The composition according to claim 1, wherein said composition is in the form of a round tablet.

42. The composition according to claim 41, wherein said tablet is a round tablet having a diameter of about 20 mm.

43. An oral pharmaceutical tablet composition comprising an effective amount of crystalline amlodipine free base and at least one pharmaceutically acceptable excipient; wherein said tablet leaves an average residue of amlodipine on the tablet punch of 0.7 $\mu g \cdot cm^{-2}$ per tablet or less.

49. The pharmaceutical composition according to claim 43, wherein said crystalline amlodipine free base is Form I crystalline amlodipine free base.

Evidence Appendix

Rule 1.132 Declaration of Ing. Arlette Vanderheijden, filed April 16, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Jacobus M. LEMMENS *et al.*	:	Examiner: A. PULLIAM
Serial No.:	10/024,520	:	Group: 1615
Filed:	December 21, 2001	:	
For:	AMLODIPINE FREE BASE		

DECLARATION UNDER 37 C.F.R.§ 1.132

I, Ing. Arlette Vanderheijden, do hereby declare as follows:

1. I am an employee of the assignee in the above-identified U.S. patent application.
2. In 1995 I completed my Higher Laboratory Education (Hoger Laboratorium Onderwijs) studies at Hogeschool Heerlen[1], in Sittard, The Netherlands in Organic Chemistry. I earned the title, "Ing." which I believe is equivalent to a Bachelor of Science degree in the U.S.
3. In 1997 I became employed by Synthon BV, the assignee of the present application, and have remained so to the present. I am presently a project manager and part of my responsibilities includes studying amlodipine pharmaceutical compositions.
4. I am aware that the Examiner has rejected the claims in the above-identified patent application over Lazar et al, U.S. Patent 5,155,120 (Lazar) with additional reliance upon Davison et al, U.S. Patent 4,879,303 (Davison). I further understand that the Examiner's position is that Lazar teaches a pharmaceutical composition that contains amlodipine base, albeit the form of the amlodipine base is not described and the clinical studies disclosed therein actually do not use the base but instead use the salt amlodipine benzenesulfonate (see column 3, lines 29-30 of Lazar). Davison mentions a composition containing amlodipine base but does not disclose the form of the base or the manufacture/isolation of the base in solid form.

[1] The School has since changed its name to Hogeschool Zuyd.

5. In order to show that the solid form of the amlodipine base effects the tabletting properties, the following experiments were carried out under my supervision and control.
6. Four samples of amlodipine free base were prepared; namely crystalline amlodipine free base Form I, crystalline amlodipine free base Form II, crystalline amlodipine free base "Form III,"[2] and amorphous amlodipine free base. The preparation of these forms is shown in Appendix A.
7. The amlodipine free base Form II contained large lumps unsuitable for tabletting and was therefore sieved (manually) over an 850 μm Retsch sieve, before blending with the other excipients. The amlodipine free base Form III contained large and hard lumps unsuitable for tabletting and was therefore milled in a Fritsch P14 Pulverisette 0.5 mm sieve, before blending with the other excipients.
8. The amorphous amlodipine free base was incapable of being blended or tabletted as shown in the pictures in Appendix B. Photo 1 shows the yellow, sticky amorphous amlodipine free base that was isolated. Photos 2 and 3 show that the amorphous amlodipine free base does not blend with the excipient in order to form a tablettable blend.
9. The stickiness of tablets using the various forms of amlodipine free base were evaluated using the following tablet formula:

Amlodipine free base	3.67 %
Microcrystalline cellulose	48.2 %
Calcium sulphate dihydrate	48.2 %
Total	100 %

The tablet preparation comprised mixing the amlodipine free base, the microcrystalline cellulose and the calcium sulphate dihydrate in a Bohle VMA 10 high shear blender. The excipients were mixed for 40 minutes at 40 rpm with the chopper off. The powder blend was compressed on a

[2] This sample is crystalline but does not appear to be pure Form I or Form II. For simplicity I refer to it as Form III, although it may not in fact be a different crystalline polymorph.

Korsch EK0 Excenter Press into tablets with 20 mm round flat punches, having a hardness of approximately 250N.

10. After compression of 50 tablets, the tablet punches were removed from the tabletting machine. The tablet material that was sticking to the tablet punches was extracted from the punches using methanol and an ultrasonic bath. This procedure was repeated for runs of 100, 150, 200, 250 and 300 tablets. The extracts together with amlodipine calibration samples were measured spectrometrically, at 237 nm. The amount of amlodipine in the samples was calculated from the calibration curve and the total amount of amlodipine extracted from both the upper and lower punch was plotted against the amount of tablets made. An average value for stickiness was calculated from the slope of the regression line by forcing the y-intercept of the line through zero. The results are summarized below:

Type of Amlodipine Free Base in Tablet	Average Stickiness
Form I	0.07 μg ADP.cm^{-2}.tablet^{-1}
Form II	2.93 μg ADP.cm^{-2}.tablet^{-1}
Form III	0.10 μg ADP.cm^{-2}.tablet^{-1}
Amorphous	Not Capable of Tabletting

11. From the above results and the pictures in Appendix B it is clear to me that crystalline forms of amlodipine free base are much more suitable for making pharmaceutical compositions than an amorphous form, which is totally unsuitable.
12. Lazar and Davison both list Pfizer Inc. as the assignee. Recently a new patent, U.S. 6,680,334 to Bentham et al (Bentham) was issued that also recites Pfizer Inc. as the assignee. Bentham explains that the original Pfizer in-house material was unsuitable for formulating. A crystalline material, preferably one that is "free from amorphous free base" is preferred (See Bentham column 3 lines 19-21). From the disclosure in Bentham, I understand that the original Pfizer amlodipine free base material was at least partially amorphous and that is why the tabletting test

in Davison showed the free base as being sticky to punches. In contrast, crystalline amlodipine free base can be very unsticky, i.e. show good punch release characteristics.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements based on information and belief are believed to be true and further that these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under section 1001 of Title 18 of the United States Code and that such false statements may jeopardize the validity of the application or any patent issuing thereon.

AVandenheijden
Ing. Arlette Vanderheijden

07-04-2004
Date

Appendix A

1. Preparation of Amlodipine Free Base Form I

Amlodipine free base Form I was prepared as follows:

Reaction scheme:

Amlodipine free base (crude) —(1) EtOH, (2) H_2O→ Amlodipine free base Form I

Starting materials:	FW	Amount	Mol	Ratio
amlodipine free base	408.88	117 g	0.286	1

Reagents and solvents:

ethanol	1080 ml

117 g of crude amlodipine free base was dissolved in 1080 ml of boiling ethanol. Then, 2160 ml water was added and the mixture was left to cool to room temperature. During cooling, a solid started to precipitate. The mixture was cooled on an ice-bath for 1 hour. The solid was isolated by filtration and washed with 180 ml water. The solid was dried in a vacuum oven at 40 °C.

Isolated yield: 98.2 gram (84%)

2. Preparation of Amlodipine Free Base Form II

Amlodipine free base Form II was prepared as follows:

Reaction scheme:

Amlodipine free base (crude) —(1) toluene, (2) *n*-hexane→ Amlodipine free base Form II

Starting materials:	FW	Amount	Mol	Ratio
amlodipine free base	408.88	110.5 g	0.270	1

Reagents and solvents:

Toluene	425 ml
n-hexane	5100 ml

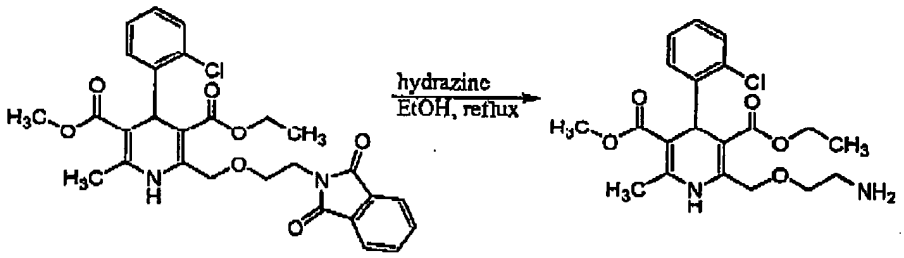
110.5 g of crude amlodipine free base was dissolved in 425 ml of boiling toluene. This solution was added slowly in 15 minutes to a 0-3 °C solution of 5100 ml *n*-hexane under stirring. During the addition, the temperature of the n-hexane solution was kept below 3 °C. The solid was filtered off and dried under vacuum at ambient temperature.

Isolated yield: 103.85 gram (94%).

3. Preparation of Amlodipine Free Base Form III

Amlodipine free base Form III was prepared as follows:

Reaction scheme:



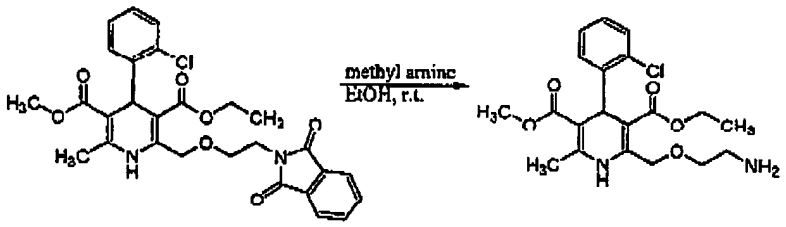
Starting materials:	FW	Amount	Mol	Ratio
phtalodipine	538.98	191.5 g	0.355	1
Reagents and solvents:				
Ethanol		2000 ml		
hydrazine monohydrate	50.06	53.4 g	1.067	3
dichloromethane		1000 ml		

191.5 g of phtalodipine (4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-2-(2-phtalimidoethoxy)methyl-1,4-dihydropyridine was stirred in 2000 ml refluxing ethanol containing 53.4 g hydrazine monohydrate. After 2 hours, the reaction mixture was cooled and filtered. The filtrate was evaporated and the residue was dissolved in 1000 ml dichloromethane and the solution was washed with 1000 ml water. The organic layer was evaporated to dryness and dried until constant weight.

Isolated yield: 116.61 gram (80 %)

4. Preparation of Amorphous Amlodipine Free Base

Reaction scheme:



Starting materials:	FW	Amount	Mol	Ratio
phtalodipine	538.98	160.0 g	0.297	1

Reagents and solvents:

33% ethanolic methyl amine	2000 ml
industrial methylated spirits	600 ml

160.0 g of phtalodipine (4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-2-(2-phtalimidoethoxy)methyl-1,4-dihydropyridine was stirred in 2000 ml 33% ethanolic methylamine solution at room temperature for three hours. The solvent then was evaporated and the residue was slurried in 600 ml industrial methylated spirits, and then filtered. The filtrated was concentrated at reduced pressure to dryness.

Isolated yield: about 120 g (quantitative yield).

Appendix B

Photo 1
Amorphous Amlodipine Free Base

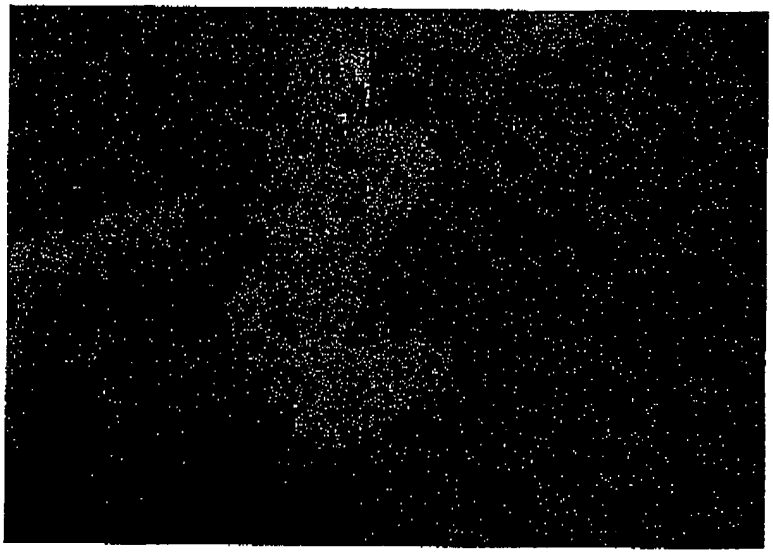


Photo 2
Amorphous Amlodipine Mixed with Excipient

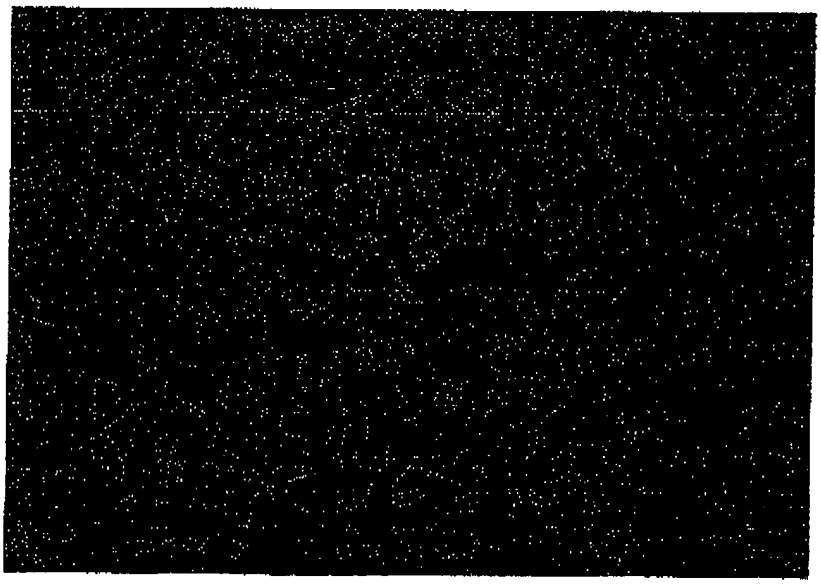
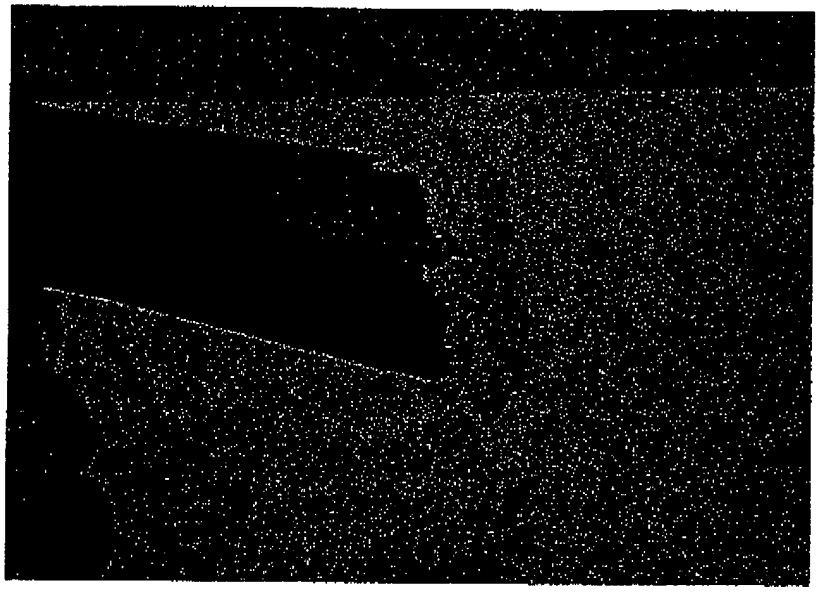


Photo 3
Amorphous Amlodipine Mixed with Excipient



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